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ORIGINAL ARTICLE

Responsiveness to Platelet Transfusions in Pediatric Patients with Thrombocytopenia: Incidence, Clinical Variables

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SUMMARY

Background: **Refractoriness to platelet transfusion has not been adequately studied in pediatric patients with thrombocytopenia. Our objectives were: (1) to describe the practice of platelet transfusion in pediatric patients with thrombocytopenia of various etiologies; (2) to assess the responsiveness to platelet transfusions and clinical variables affecting platelet transfusions response; and (3) to evaluate incidence of PTR.**

Methods: **A retrospective study included pediatric patients with thrombocytopenia admitted to a tertiary children's hospital who received ≥ 1 platelet transfusion during hospitalization. Responsiveness was measured by corrected count increment (CCI), poor platelet transfusion response (PPTR), and platelet transfusion refractoriness (PTR).**

Results: **A total of 334 patients were eligible for the study and received 1,164 transfusions, with a median of 2 (IQR: 1 - 5) platelet transfusions. Patients admitted with hematologic malignancies had the highest median number of platelet transfusions (5, IQR: 4 - 10). The median CCI of 1,164 platelet post-transfusions was 17.0 (IQR: 9.4 - 24.6) and the incidence of PPTR was 11.9%. Patients admitted with ITP had the lowest median CCI (7.6, IQR: 1.0 - 12.5) and the highest incidence of PPTR (36.4%, 8/22). Older age of platelet components, low doses of platelet transfusion, increasing number of platelet transfusions (≥ 5), splenomegaly, bleeding, DIC, shock, ECMO supported, and HLA antibody-positive were independent risk factors for PPTR. Finally, the incidence of PTR was 11.4%.**

Conclusions: **Practical experience of clinicians regarding the use of apheresis platelets in pediatric patients is determined. Highlight that PTR is not a low probability event when apheresis platelets are received in pediatric patients.**

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Supplementary Data

Table S1. Pediatric demographic data and transfusion details during study period.

Characteristics	Overall (n = 334)	Acute bleeding (n = 14)	Cardiac surgery (n = 24)	Hematologic malignancies (n = 63)	Acute severe pneumonia (n = 13)	ITP (n = 13)	Liver failure (n = 9)	Other Malignancies [a] (n = 64)	Sepsis/ DIC (n = 9)	Neuroblastoma (n = 79)	Others [b] (n = 46)
Gender (n, %)											
Female	139 (41.6.)	3 (21.4)	8 (33.3)	26 (41.3)	4 (30.8)	6 (46.2)	4 (44.4)	30 (46.9)	5 (55.6)	36 (45.6)	17 (37.0)
Male	195 (58.4)	11 (78.6)	16 (66.7)	37 (58.7)	9 (69.2)	7 (53.8)	5 (55.6)	34 (53.1)	4 (44.4)	43 (54.4)	29 (63.0)
Age (y), median (IQR)	3.4 (0.8 - 6.0)	4.5 (1.6 - 7.7)	0.1 (0.1 - 0.7)	6.0 (4.1 - 11.0)	0.6 (0.2 - 2.6)	0.1 (0.1 - 1.6)	2.9 (0.9 - 7.0)	3.9 (2.0 - 8.0)	0.04 (0.02 - 0.06)	4.3 (2.8 - 6.0)	0.1 (0.1 - 2.0)
< 1 month	47 (14.1)	2 (14.3)	10 (41.7)	0 (0.0)	2 (15.4)	5 (38.5)	0 (0.0)	1 (1.6)	8 (88.9)	0 (0.0)	19 (41.3)
1 - 12 months	43 (12.9)	0 (0)	9 (37.5)	0 (0.0)	6 (46.2)	5 (38.5)	3 (33.3)	2 (3.1)	1 (11.1)	4 (5.1)	13 (28.3)
1 - 6 years	149 (44.6)	7 (50.0)	3 (12.5)	28 (44.4)	4 (30.8)	2 (15.4)	4 (44.4)	42 (65.6)	0 (0.0)	54 (68.4)	7 (15.2)
6 - 12 years	74 (22.2)	3 (21.4)	2 (8.3)	26 (41.3)	1 (7.7)	1 (7.7)	2 (22.2)	16 (25.0)	0 (0.0)	20 (25.3)	3 (6.5)
12 - 18 years	21 (6.3)	2 (14.3)	0 (0.0)	9 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	3(4.7)	0 (0.0)	1 (1.3)	4 (8.7)
Patient ABO group (n, %)											
A	95 (28.4)	5 (35.7)	11 (45.8)	21 (33.3)	6 (46.2)	1 (7.7)	3 (33.3)	21 (32.8)	2 (22.2)	11 (13.9)	14 (30.4)
B	105 (31.4)	3 (21.4)	7 (29.2)	19 (30.2)	4 (30.8)	6 (46.2)	1 (11.1)	20 (31.3)	5 (55.6)	27 (34.2)	13 (28.3)
O	108 (32.3)	4 (28.6)	4 (16.7)	19 (30.2)	3 (23.1)	5 (38.5)	5 (55.6)	19 (29.7)	2 (22.2)	32 (40.5)	15 (32.6)
AB	26 (7.8)	2 (14.3)	2 (8.3)	4 (6.3)	0 (0.0)	1 (7.7)	0 (0.0)	4 (6.3)	0 (0.0)	9 (11.4)	4 (8.7)
Number of platelet transfusions, median (IQR)	2.0 (1 - 5)	1.0 (1 - 2)	1.0 (1 - 3)	5.0 (4 - 10)	1.0 (1 - 5)	1.0 (1 - 2)	1.0 (1 - 3)	2.0 (1 - 5)	1.0 (1 - 2)	2.0 (1 - 6)	1.0 (1 - 2)
Number (%) of patient with:											
1 Platelet transfusion	141 (42.2)	9 (64.3)	15 (62.5)	3 (4.8）	7 (53.8)	10 (76.9)	5 (55.6)	27 (42.2)	7 (77.8)	25 (31.6)	33 (71.7)
2 Platelet transfusions	48 (14.4)	2 (14.3)	3 (12.5)	2 (3.2)	2 (15.4)	1 (7.7)	1 (11.1)	14 (21.9)	1 (11.1)	16 (20.3)	6 (13.0)
3 Platelet transfusions	34 (10.2)	2 (14.3)	3 (12.5)	9 (14.3)	0 (0.0)	0 (0.0)	2 (22.2)	5 (7.8)	1 (11.1)	10 (12.7)	2 (4.4)
4 Platelet transfusions	23 (6.9)	1 (7.1)	1 (4.2)	12 (19.0)	1 (7.7)	1 (7.7)	0 (0.0)	2 (3.1)	0 (0.0)	4 (5.1)	1 (2.2)
≥ 5 Platelet transfusions	88 (26.3)	0 (0.0)	2 (8.3)	37 (58.7)	3 (23.1)	1 (7.7)	1 (11.1)	16 (25.0)	0 (0.0)	24 (30.4)	4 (8.7)
Total number of platelet transfusions (n)	1,164	23	46	438	31	22	20	194	12	292	86
Pre-transfusion platelet counts (x 10^9/L), Median (IQR)	10 (6 - 18)	30 (18 - 37)	42 (28 - 57)	8 (5 - 13)	20 (11 - 41)	8 (6 - 15)	14 (4 - 35)	11 (6 - 19)	24 (19 - 30)	9 (5 - 14)	23 (12 - 36)

Table S1. Pediatric demographic data and transfusion details during study period (continued).

Characteristics	Overall (n = 334)	Acute bleeding (n = 14)	Cardiac surgery (n = 24)	Hematologic malignancies (n = 63)	Acute severe pneumonia (n = 13)	ITP (n = 13)	Liver failure (n = 9)	Other Malignancies [a] (n = 64)	Sepsis/ DIC (n = 9)	Neuroblastoma (n = 79)	Others [b] (n = 46)
Breakdown of pre-transfusion platelet counts (x 10^9/L), (n, %)											
0 - 10	615 (52.8)	2 (8.7)	0 (0.0)	287 (65.5)	6 (19.4)	15 (68.3)	8 (40.0)	94 (48.5)	0 (0.0)	183 (62.7)	20 (23.3)
11 - 20	302 (25.9)	5 (21.7)	6 (13.0)	110 (25.1)	11 (35.5)	5 (22.7)	5 (25.0)	56 (28.9)	5 (41.7)	79 (27.0)	20 (23.3)
21 - 50	205 (17.6)	15 (65.2)	23 (50.0)	39 (8.9)	9 (29.0)	1 (4.5)	6 (30.0)	39 (20.1)	7 (58.3)	28 (9.6)	38 (44.2)
51 - 80	42 (3.6)	1 (4.3)	17 (37.0)	2 (0.5)	5 (16.1)	1 (4.5)	1 (5.0)	5 (2.5)	0 (0.0)	2 (0.7)	8 (9.2)
Post-transfusion platelet counts (x 10^9/L), Median (IQR)	51 (34 - 75)	65 (34 - 104)	118 (73 - 201)	44 (28 - 64)	51 (30 - 122)	28 (8 - 57)	43 (24 - 76)	55 (40 - 78)	77 (60 - 117)	49 (35 - 71)	65 (46 - 93)

Abbreviations: N - the number of patients within each subgroups, n - the number of platelet transfusions in patient subgroups categorized, y - years, IQR - interquartile ranges, ITP - idiopathic thrombocytopenic purpura. [a] - Other malignancies include: embryonal tumor, brain stem tumor, medulloblastoma, hepatoblastoma, adrenal malignancy, nephroblastoma, clear cell renal sarcoma, ovarian cancer. [b] - Others include: necrotizing enterocolitis (NEC), neonatal respiratory distress syndrome, neonatal respiratory failure, neonatal asphyxia, hemophagocytic syndrome, Crohn's disease.

Table S2. Univariate analysis identified the factors for the PPTR in patients.

Total, n (%)	1,026 (88.1)	138 (11.9)	
Patients-related			
Gender, n (%)			
Male	586 (57.1)	85 (61.6)	
Female	440 (42.9)	53 (38.4)	0.317
Age (y), median (IQR)	4.1 (2.2 - 8.0)	4.3 (1.9 - 10.0)	0.317
WBC (x 10^9/L), median (IQR)	0.97 (0.32 - 4.09)	2.52 (0.53 - 6.95)	0.002 **
CRP (mg/L), median (IQR)	7.66 (1.35 - 28.90)	9.72 (1.05 - 42.09)	0.410
Platelets-related			
ABO group, n (%)			
A	295 (28.6)	38 (27.5)	
B	333 (32.5)	47 (34.1)	
O	322 (31.4)	44 (31.9)	
AB	76 (7.5)	9 (6.5)	0.960
Age of platelet components (days), median (IQR)	0.34 (0.19 - 1.27)	1.14 (0.25 - 1.97)	0.016 *
Platelet dose (/m^2), n (%)			
LD (≤ 1.1 x 10^{11})	19 (1.9)	10 (7.2)	
MD and HD (> 1.1 x 10^{11})	1,007 (98.1)	128 (92.8)	0.001 **
Number of transfusions (≥ 5), n (%)			
Yes	324 (31.6)	58 (42.0)	
No	702 (68.4)	80 (58.0)	0.014 *

Table S2. Univariate analysis identified the factors for the PPTR in patients (continued).

Variables	Non-PPTR	PPTR	p-value
Clinical-related			
Non-immune factors			
Infection, n (%)			
Sever	**24 (2.3)**	**7 (5.1)**	
Minor	**66 (6.4)**	**15 (10.9)**	
No	**936 (91.2)**	**116 (84.1)**	**0.023** *
Splenomegaly, n (%)			
Yes	**63 (6.1)**	**26 (18.8)**	
No	**963 (93.9)**	**112 (81.2)**	**< 0.001** ***
Fever, n (%)			
Yes	**170 (16.6)**	**32 (23.2)**	
No	**856 (83.4)**	**106 (76.8)**	**0.050**
Bleeding, n (%)			
Yes	**87 (8.5)**	**25 (18.1)**	
No	**939 (91.5)**	**113 (81.9)**	**< 0.001** ***
Sepsis, n (%)			
Yes	**5 (0.5)**	**0 (0.0)**	
No	**1,021 (99.5)**	**138 (100.0)**	**1.000**
DIC, n (%)			
Yes	**4 (0.4)**	**6 (4.3)**	
No	**1,022 (99.6)**	**132 (95.7)**	**< 0.001** ***
Shock, n (%)			
Yes	**3 (0.3)**	**6 (4.3)**	
No	**1,023 (99.7)**	**132 (95.7)**	**< 0.001** ***
ECMO supported, n (%)			
Yes	**19 (1.9)**	**7 (5.1)**	
No	**1,007 (98.1)**	**131 (94.9)**	**0.036** *
CIM, n (%)			
Yes	**434 (42.3)**	**44 (31.9)**	**0.020** *
No	**592 (57.7)**	**94 (68.1)**	
Immune factors			
HLA antibody-positive, n (%)			
Yes	**29 (2.8)**	**10 (7.2)**	
No	**997 (97.2)**	**128 (92.8)**	**0.014** *

Abbreviations: y - years, PPTR - poor platelet transfusion response, IQR - interquartile range, WBC - white blood cell counts, CRP - C-reactive protein, LD - low doses, MD and HD - medium and high doses, DIC - disseminated intravascular coagulation, ECMO - extracorporeal membrane oxygenation, CIM - chemotherapy-induced myelosuppression. * - p < 0.001; ** - p < 0.01; * - p < 0.05.**

Table S3. Correlation between variables and CCI using Pearson's correlation coefficient in platelet transfusions.

Variables	（20 - 24）h-CCI	
	r (correlation coefficient)	p-value
Gender (female)	0.001	0.971
Age (y)	-0.004	0.895
WBC (x 10^9/L)	-0.020	0.499
CRP (mg/L)	-0.094	0.001 **
Age of platelet components (days)	-0.039	0.189
Platelet transfusion dose (/m^2)	0.025	0.387
Number of transfusions (≥ 5)	-0.051	0.084
Infection	-0.143	< 0.001 ***
Splenomegaly	-0.243	< 0.001 ***
Fever	-0.132	< 0.001 ***
Bleeding	-0.119	< 0.001 ***
Sepsis	-0.016	0.584
DIC	-0.111	< 0.001 ***
Shock	-0.117	< 0.001 ***
ECMO supported	-0.103	< 0.001 ***
CIM	0.009	0.769
HLA antibody-positive	-0.055	0.060

Abbreviations: 20 - 24 hour CCI - 20 - 24 hour corrected count increment, WBC - white blood cell counts, CRP - C-reactive protein, DIC - disseminated intravascular coagulation, ECMO - extracorporeal membrane oxygenation, CIM - chemotherapy-induced myelosuppression.
***** - p < 0.001; ** - p < 0.01; * - p < 0.05.**

Table S4. Clinical characteristics of patients experiencing platelet transfusion refractoriness.

Case	Gender	Age	ABO Group	Platelet transfusion dose (/m^2)	Number of PTR events/Number of transfusions	Detail primary diagnosis	Clinical factors
1	female	4.8 Y	O	M	2/10	lymphoma	splenomegaly; fever
2	female	7 M	B	M	1/2	NBL	CIM
3	female	15 D	B	H	2/3	ASD	ECMO supported
4	female	3.3 Y	AB	M	1/2	JMML	splenomegaly
5	male	11.0 Y	B	L	2/3	ITP	splenomegaly
6	male	11.0 Y	AB	M	1/9	Intracranial bleeding	bleeding (brain)
7	female	18 D	O	M	3/6	ITP	bleeding (Brain); HLA antibody-positive
8	female	9.0 Y	O	M	3/7	NBL	splenomegaly; fever; CIM
9	male	1.2 Y	B	M	1/9	adrenal tumor	none
10	male	2 D	A	H	2/5	hemangiomas	bleeding (skin)
11	male	1.9 Y	A	M	1/8	hepatoblastoma	bleeding (digestive tract); fever
12	male	2.6 Y	B	M	2/11	NBL	bleeding (skin); fever; CIM

Table S4. Clinical characteristics of patients experiencing platelet transfusion refractoriness (continued).

Case	Gender	Age	ABO Group	Platelet transfusion dose (/m^2)	Number of PTR events/Number of transfusions	Detail primary diagnosis	Clinical factors
13	male	10.0 Y	B	M	1/7	brain tumor	bleeding (nose) ; CIM
14	male	10.0 Y	A	M	1/2	sepsis and DIC	septic shock; infection
15	male	10.0 Y	A	M	2/3	severe closed craniocerebral injury	hemorrhagic shock
16	male	3.8 Y	B	M	2/16	ALL-L2	none
17	female	11.0 Y	B	L	5/15	ALL-L2	fever; CIM
18	male	14.0 Y	O	L	3/18	AML-M4	fever; CIM
19	male	4.7 Y	A	M	1/5	SAA	HLA antibody-positive
20	male	2.2 Y	A	M	2/23	ALL-L2	septic shock; infection; CIM
21	male	5.8 Y	A	M	3/13	fanconi anemia	bleeding (skin); DIC
22	male	12.0 Y	B	L	1/7	ALL	infection; CIM

Abbreviations: Y - years, M - months, D - days, NBL - neuroblastoma, ASD - Atrial Septal Defect, JMML - juvenile myelomonocytic leukemia, ITP - Immune thrombocytopenic purpura, ALL - acute lymphocytic leukemia, AML - acute myeloid leukemia, SAA - severe aplastic anemia, CIM - chemotherapy-induced myelosuppression, ECMO - extracorporeal membrane oxygenation, DIC - disseminated intravascular coagulation.

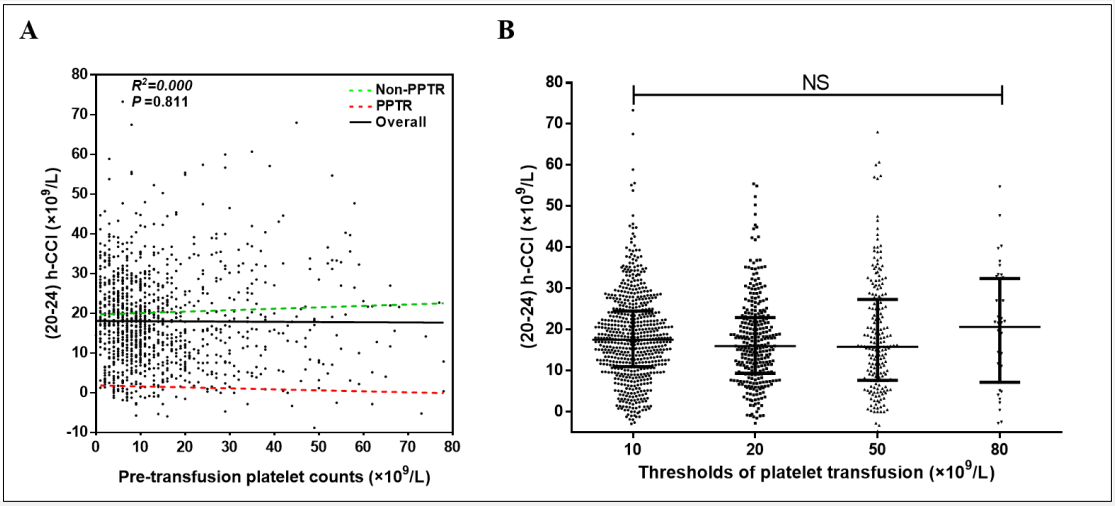

Figure S1. (A) The correlation between CCI and pre-transfusion platelet counts and (B) comparison of between CCI and different platelet transfusion thresholds.

In each part of this figure, the CCI is plotted versus the pre-transfusion platelet counts and different platelet thresholds. (A) The equations for the regression lines are overall: 18.10 - 0.005437 * pre-transfusion platelet counts; non-PPTR: 19.73 + 0.03589 * pre-transfusion platelet counts; PPTR: 1.884 - 0.02489 * pre-transfusion platelet counts. The regression line for the overall is plotted as a solid line for comparison with the regression line for the non-PPTR and PPTR shown as the dotted line. (B) The middle thin line, lower and upper end line represent the median value, the 25th and 75th percentiles, respectively. CCI, 20 - 24 hour corrected count increment.